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A Guide to Capturing and Managing Data in Digital Therapeutics Trials



This guide explores the DTx clinical trial landscape and offers guidance on a data collection strategy and system solutions for DTx manufacturers.

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Digital therapeutics (DTx) is one of the newest subsets of digital health and delivers evidence-based, clinical-grade therapeutic interventions to prevent, manage, or treat a medical disorder or disease. Used alone or with other medications, devices, or therapies, DTx focuses on a range of medical conditions and supports various stages of the traditional health care process. Digital therapeutics can also address unmet patient needs that traditional treatments and therapies do not.

DTx requires clinical evidence and real-world outcomes to gain regulatory clearance or approval, just like drug and medical device therapies. Once DTx manufacturers determine their path to commercialization, their success depends on implementing an effective data collection strategy to support the particular challenges of DTx studies, including a lack of standardization and a vast amount of data collected from disparate sources.

This guide explores the DTx clinical trial landscape and offers guidance on a data collection strategy and system solutions for DTx manufacturers.

Overview of DTx Challenges

DTx manufacturers face unique challenges bringing their therapies to market, including:

- DTx are erroneously considered a subset of over-the-counter wellness applications, despite their distinct and crucial differences.
- The current approval framework relies on drug commercialization models rather than a model specific to DTx.
- DTx companies are often emerging and lack the resources to sustain the average ten-year timeline and approximate $2.6B cost for a traditional randomized clinical trial (RCT).
- Reimbursement of DTx from payers is not yet widespread.

How do DTx differ from wellness applications?

DTx are often associated with wellness applications that fall under “digital health,” but they differ significantly. DTx directly affect health outcomes rather than merely providing feedback and information or track a participant’s behavior or condition. General wellness applications do not require a prescription, nor do they require regulation from the U.S. Food & Drug Administration (FDA), whereas some DTx do.

DTx manufacturers need to distinguish their therapies from general wellness apps to provide incentives for providers, payers, and pharmaceutical companies to adopt them. In particular, many health and wellness apps promote unsubstantiated claims about their clinical benefits, furthering doubts about the validity of DTx among consumers and healthcare professionals. These doubts, in turn, create a barrier to acceptance and reimbursement.

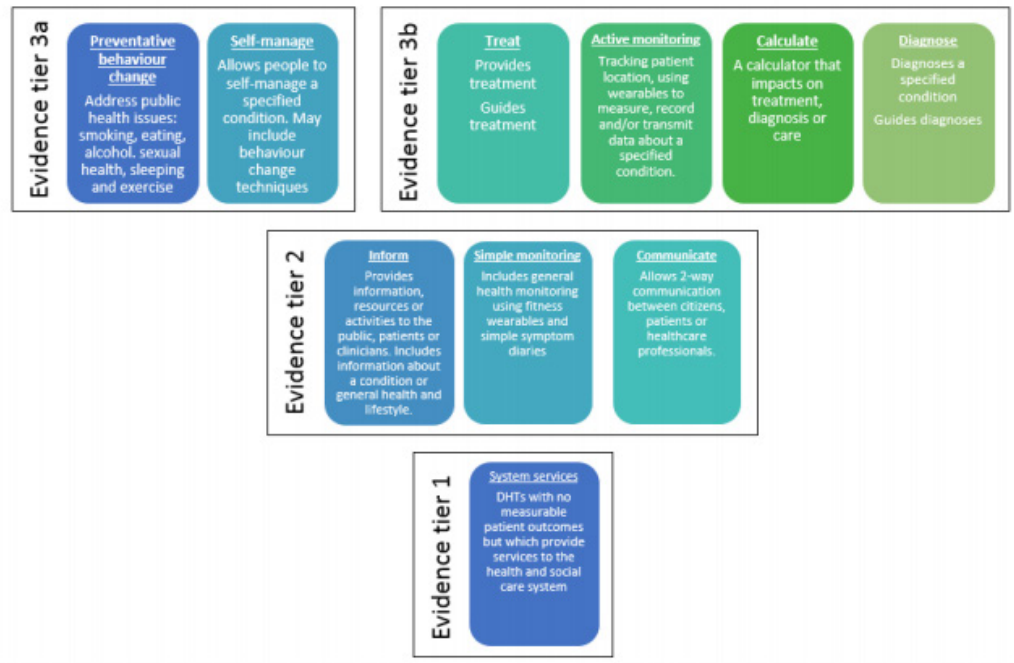
How are DTx regulated?

The Software as a Medical Device (SaMD) framework, developed by the International Medical Device Regulators Forum (IMDRF), regulates most DTx. Regulatory agencies update these regulatory frameworks to support the development, evaluation, and, when warranted, novel DTx clearance.
In particular, both the U.S. and U.K. regulatory bodies have recently made key updates for DTx:

- In August 2017, the FDA launched its Software Precertification (Pre-Cert) Pilot program, which provides more streamlined and efficient regulatory oversight of software-based medical devices. This program is part of its Digital Health Innovation Action Plan, whose goal is timely patient access to high-quality, safe, and effective digital health products.

- In the U.K., the National Institute for Health and Care Excellence (NICE) created a framework for evidence standards for digital health technologies (DHTs). The technologies are classified by function and stratified into evidence tiers.

Figure 1 DHTs classified by function and stratified into evidence tiers



Evidence Standards Framework for Digital Health Technologies (March 2019)
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The future of DTx regulation

While regulatory bodies are moving forward, the regulatory pathway for DTx is still new and not yet tailored for these treatments' unique needs. The FDA recognizes the need for an agile approach that allows these products to be frequently updated. This ongoing gray area for regulation and path to approval leaves DTx manufacturers somewhat on their own as they navigate an often-uncharted course.

They face significant regulatory challenges, including:

- Time to market. Development cycles in digital health technologies are much shorter than those for medical devices (which are, in turn, shorter than those for drug cycles). Often an outdated version of the product already exists by the time of regulatory approval.

- Lack of global uniformity. Implementation differences in the EU on a country-by-country basis create a fragmented market, complicating the creation of a uniform regulatory framework.

- Requirements in flux. Newer regulations, such as the European Union Medical Device Regulation, which requires strict clinical evidence, may change DTx approvals' requirements in unanticipated ways.

To further develop an acceptable regulatory framework, DTx manufacturers should set new industry precedents with approaches that reduce costs and shorten timelines.



How do payers reimburse DTx?

DTx can demonstrate value to payers with two key features: First, DTx's ability to capture real-world data on usage, engagement, disease progression, healthcare outcomes, and therapeutic efficiency; and second, DTx can offer less expensive and/or more effective therapies. In the U.S., many health plans have launched initiatives to help provide their members with access to digital health services, but there is still a lack of widespread adoption.

In regard to leading payer adoption for DTx, Express Scripts, a pharmacy benefit manager, announced in May 2019 that it was developing a formulary for digital health solutions. By December 2019, it had selected its first 15 products to include in the formulary. To date, Express Scripts is one of the few significant payers to make this move.

Commercialization strategies

Commercialization for DTx typically follows one of two routes: traditional or novel. Because of the emerging (and often confusing) regulatory landscape around DTx, the route choice is more incumbent on the DTx manufacturer's preference for commercialization path, rather than any product designation, such as risk level or class.

1. The **traditional route** is the same one drug approvals take: DTx manufacturers run a trial, submit for FDA approval, and, upon approval and commercialization, gather post-market data to inform existing clinical claims' adjustments or find new clinical claims. This route is tried and true, but also expensive and time-consuming.

2. The **novel route** involves manufacturers immediately commercializing a product under a general wellness claim instead of running a clinical trial, and then gathering post-market data from users. The data then feed into the modification or change of clinical claims to prepare for FDA approval. This route provides the advantage of taking the product to market and generating revenue much sooner.

Remember, DTx fall under the SaMD regulatory framework: if a sponsor has a novel therapeutic, it must run a clinical trial to use the novel pathway with no predicate.

Also, note the distinctions between FDA-approved and FDA-cleared:

- "Approved" indicates that the device completed an FDA Premarket Approval (PMA) evaluating Class III high-risk products' safety and effectiveness.
- "Cleared" suggests that the device completed a 510(k) pathway for lower risk-level products.

Finally, in 2020 the FDA changed its emergency use authorization guidance and temporarily removed requirements for digital health tools to accelerate their time to market during the COVID-19 pandemic. The FDA has not yet indicated how long these measures will remain in place.

DTx clinical trials

The definition of DTx does not stipulate mandatory clinical trials, so the decision to conduct one is often strategic. Manufacturers conduct clinical trials to produce validated outcomes so that payers regard them as legitimate and support a straightforward coverage evaluation process more like that of the drug approval pathway. Trial outcomes should therefore translate into stakeholder value (for example, efficacy and health economics advantages). Payers will also value a regulator's stamp of approval.

Reasons to do a clinical trial include the opportunity to

- Establish a clinical claim
- Gain better access to populations that fall under a DTx clinical claim
- Acquire FDA approval to facilitate third-party endorsement
- Achieve a competitive advantage in the marketplace

Manufacturers need to balance trial benefits with accelerating commercialization. In addition, for some manufacturers, the cost of a traditional clinical trial might be prohibitive.

What are the differences between DTx trials and drug trials?

At their core, DTx are technology-based. As a result, there are fundamental differences between DTx clinical trials and traditional drug trials. Specifically, in a DTx trial:

- Digital endpoints are highly relevant because the data generated are from digital products.
- Participant (or patient) engagement is essential because participants are often home-based and may be self-administering the therapeutic.
- On-site participation needs may be minimal because the participants engage primarily with the technology, which can be done anywhere.
- Data capture can occur in real-time with the appropriate Electronic Data Capture (EDC) System.
- Randomization and blinding can be a challenge. For example, when testing a DTx mobile app, it may be difficult to determine how to create an alternative DTx without developing a whole new app.

In terms of data collection, key differences include:

- The digital therapeutic itself will collect information.
- Input and output often occur on the same device. This way, manufacturers can merge collection and analysis into one framework.
- There will likely be a higher rate and volume of data to manage.

With this particular set of factors, a DTx trial is an excellent fit for decentralized clinical trial technology.



What are the challenges of DTx clinical trials?

As with any emerging and novel technology, DTx clinical trials present unique challenges. The good news is that with careful planning, manufacturers can often alleviate or even circumvent them entirely. Here are some key challenges to consider, along with possible solutions:

- **Controls and placebos are difficult to define.** Initiate early discussions with the relevant regulatory body(ies) about an acceptable control/placebo for a sponsor's study.

- **Primary endpoints must be accessible at home and participant-centric.**

- **Security requirements are high in a decentralized environment** (from such key factors as using multiple vendors and data stored in different cloud-based architectures). Choosing technology with strong cybersecurity is essential.

- **The regulatory environment is continually changing.** To be successful, rely on the existing guidance but stay updated with regulatory guidelines, as they may be subject to change.

- **With fewer or no sites, participant recruitment does not follow the model of proximity.** Use registries, advocacy groups, EMR, prescription databases, mobile, and social media to reach out and recruit participants.

- **Participant interactions are varied and dynamic.** Invest in a centralized platform to simultaneously view real-time data and make informed decisions during the trial's execution.

Where possible, don't force your trial to follow a model designed for traditional trials. With innovative approaches, manufacturers can meet these challenges and set new industry precedents.

DTx data collection

With DTx, much of the data are real-world evidence collected directly during the participants' daily activities via apps and wearables connected to participants' devices. Digital devices improve the quality of data collected and facilitate the demographic diversity that the treatment will need to align with.

Data sources

There are potentially dozens of data sources for DTx clinical trials, including wearables, telemedicine visits, electronic informed consent (eConsent), electronic patient-reported outcomes (ePRO), and the data from the digital therapeutic itself.

Not all trials require eConsent if the application possesses a minimal risk designation, and the sponsor has acquired a waiver of consent. Re-consenting might be required, however, when performing future studies using the same data. With Castor, eConsent data such as documents and signatures are stored in the eConsent application.

Digital endpoints

Due to the nature of data collection from wearables, DTx trials entail digital endpoints. DTx manufacturers must ensure that data collected using wearables meet evidentiary requirements for regulatory submission and design appropriate end-to-end points for their studies.
Examples of data points collected with wearables include sleep, physical activity, heart rate, breathing rate, weight, blood pressure, oximetry, and gait assessment.



Data standards

Because DTx trials rely on multiple data sources, standardization becomes a critical challenge. Unstandardized data are much more difficult to analyze without costly and time-consuming data management. The lack of standards for electronic health records (EHRs) and an interoperable data ecosystem are also barriers to digital health technologies' adoption. Still, there has been recent progress:

- In February 2019, the European Commission sent a powerful signal in favor of international standards with the Recommendation for an Electronic Health Record (EHR) Exchange Format to exchange medical information across European borders.

- In 2019, MedTech Europe called for an interoperable data ecosystem for digital health.

Meanwhile, industry consortiums such as the Digital Therapeutics Alliance (DTA), a global non-profit trade association of industry leaders and stakeholders, are engaged in the evidence-driven advancement of DTx. DTA exists to broaden the understanding, adoption, and integration of clinically evaluated DTx into healthcare through education, advocacy, and research. It is spearheading the development of foundational industry definitions, best practices, and frameworks.

As the standards community moves toward recognizing DTx as a crucial player, it is all the more critical to run DTx clinical trials on a modern technology platform that effectively pulls data from multiple sources, meets industry standards, and integrates with post-market Real World Evidence (data).



Data collection technology for a DTx decentralized clinical trial

With significantly less activity occurring at sites, a DTx trial is ideal for decentralized clinical trial (DCT) technology. DCT technology includes the critical components needed to support a trial and is flexible enough to meet the requirements of today's modern apps. Additionally, DCT technology can provide cost savings by reducing site engagement and physical location requirements.

Together, these DCT components streamline processes for both participants and staff and ensure high-quality data control and management:

- **Electronic Data Capture (EDC)**. A modern EDC system provides the foundation for managing DTx clinical trial data collection. Manufacturers should choose carefully, as many of the leading EDC systems were built in the mid-2000s and cannot adapt to current DTx-based mobile apps without additional development and cost.
- **Clinical Data Management System (CDMS)** Every DTx sponsor needs a centralized system that can ingest and manage all trial and real-world post-market data.
- **Electronic patient-reported outcome (ePRO).** DTx brings the significant shift of including clinical outcomes data in regulatory premarket applications, driving the need to demonstrate participant outcomes to gain approval and reimbursement effectively. An ePRO system integrated with an EDC greatly facilitates this process. With it, staff can easily and rapidly create surveys, and participants can self-report data from any location, at any time. The ePRO also provides a viable quick start for studies newly transitioning to a DCT.
- **Application Programming Interface (API)**. Transferring data from multiple sources into an EDC can be a long and laborious process. An eClinical system with a modern and robust API built to the highest industry standards can readily ingest the necessary data types and automate the complexities.
- **eConsent**. The ability to remotely consent a participant saves time and money. It is particularly well suited for enrolling participants already using their own devices for the investigative therapy and typically increases their engagement and retention.

With the complete DCT platform, EDC + ePRO + API allows manufacturers to collect data from different sources; eConsent streamlines recruitment to enrollment; and studies are more burden-free and data-focused.

Automated user acceptance testing

User Acceptance Testing (UAT) is a critical component of clinical trials. Manufacturers must perform UAT for electronic case report form (eCRF) validation before using an EDC system. UAT is traditionally a manual and repetitive process done by multiple users, which can be time-consuming and lead to delays in studies going live.

Automated UAT for eCRF validation contributes to study success, solves sponsor/CRO data pain points, and should be considered the new gold standard for clinical research. When evaluating platforms for digital therapeutic trials, consider a vendor with services to automate UAT.

Commercialization case studies

DTx are increasingly submitted to the FDA for clearance or approval to market as prescription therapies. Let's look at some live market examples of DTx manufacturers who took different commercialization paths—traditional, novel, and FDA emergency authorization— including the first DTx product to receive FDA approval.

Traditional: RCT and FDA approval for reset from Pear Therapeutics

reSET from Pear Therapeutics is a 90-day prescription digital therapeutic (PDT) for substance use disorder (SUD). The Boston-based company worked with Sandoz Inc., a Novartis division, to receive FDA approval for reSET-O, a PDT for treating individuals with Opioid Use Disorder (OUD). As a result, reSET is the first digital therapeutic to receive FDA approval.

The Pear Therapeutics / Sandoz partnership demonstrates how DTx developers might seek partnerships with pharmaceutical companies whose expertise complements their own. With this model, the DTx company can receive such commercialization benefits as go-to-market sales support and payer negotiation expertise.

Novel: commercialized under general wellness claim for Quit Genius

Quit Genius rapidly moved to market with general wellness claims for their therapies geared at treating individuals with tobacco, opioid-use, and alcohol-use disorder through digital cognitive behavioral therapy programs. The service includes a virtual coaching platform and a connected breath sensor.
Quit Genius successfully leveraged the updated FDA regulatory requirements in 2020 during COVID-19, which expanded its program to include multiple addictions programs.

Temporary: 2020 FDA emergency authorization for Endeavor by Akili Interactive

Before the Covid-19 pandemic, Akili Interactive was well into applying for FDA clearance for its first product. The company had just completed a randomized trial of Endeavor, a video game designed to improve children's attention span with attention deficit hyperactivity disorder (ADHD).

In March 2020, the FDA temporarily waived requirements around digital health tools to provide more immediate benefit to public health due to the global pandemic. As a result, Akili released its product to the public based on the FDA's emergency guidance. The company is still actively pursuing 510(k) clearance for Endeavor but plans to offer it to the public temporarily at no cost.

Conclusion

DTx are a new category of treatment approaches that offers a significant opportunity to address chronic and other difficult-to-treat conditions and advance public health. More rigorous testing is required to achieve reliable evidence on DTx' safety and efficacy through randomized trials. DTx manufacturers have an opportunity to establish improved and more efficient pathways to bring novel therapeutics to market and advance human health.

DTx clinical trials have special needs and challenges with data collection as compared to drug trials. In a DTx trial, the data collection strategy depends on the chosen route to commercialization. Ultimately, a DTx trial's success depends on selecting the right data technology vendor. Castor is here to help.



About Castor

A global health tech company, Castor enables manufacturers and research organizations to maximize the impact of data through clinical trial automation and data reuse, while supporting a patient-centric, decentralized approach to research.

Castor's platform has supported more than 4,100 commercial and academic studies that cover a broad range of disease areas including oncology, diabetes, cardiovascular disease, central nervous system, rare diseases, and infectious diseases.

Castor's capabilities include:

Electronic Data Capture (EDC) to maximize productivity in clinical studies and integrate data from different sources

Electronic Patient Reported Outcome (ePRO) forms to administer surveys and collect clinical data into a centralized platform

Integrations to capture data directly from multiple sources, including patients, clinicians, devices, wearables, and EHR systems

eConsent to facilitate and automate patient enrollment processes

Services for study set up and study conduct to help reduce study build time, capture higher quality data, and get to market faster

